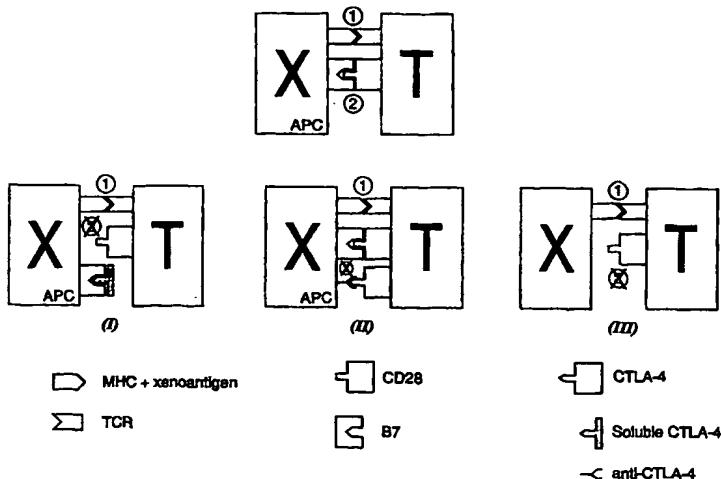




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :	A2	(11) International Publication Number: WO 99/57266
C12N 15/12, 15/13, A61K 38/17, C12N 5/10, C07K 16/28, 14/705, A01K 67/027, A61K 31/70, 39/395, 35/14, 48/00		(43) International Publication Date: 11 November 1999 (11.11.99)
<p>(21) International Application Number: PCT/GB99/01350</p> <p>(22) International Filing Date: 30 April 1999 (30.04.99)</p> <p>(30) Priority Data: 9809280.2 30 April 1998 (30.04.98) GB</p> <p>(71) Applicant (<i>for all designated States except US</i>): IMPERIAL COLLEGE INNOVATIONS LIMITED [GB/GB]; 47 Prince's Gate, Exhibition Road, London SW7 2QA (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): LECHLER, Ian, Robert [GB/GB]; Hammersmith Hospital, London W12 0NN (GB). DORLING, Anthony [GB/GB]; Hammersmith Hospital, London W12 0NN (GB).</p> <p>(74) Agent: HOWARD, Paul, Nicholas; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).</p>		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
<p>Published</p> <p><i>Without international search report and to be republished upon receipt of that report.</i></p>		

(54) Title: IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION SIGNAL 2 (B7/CD28 INTERACTION)



(57) Abstract

The invention provides means and methods for inhibiting T-cell mediated rejection of a xenotransplanted organ by blocking the delivery of co-stimulatory signal 2 (the B7/CD28 interaction) in order to prevent the activation of xenoreactive T-cells in the recipient. In a first aspect, co-stimulation is prevented by administration to the organ recipient of a soluble form of CTLA-4 from the xenogeneic donor organism. This preferentially binds B7 on the xenograft and blocks the interaction between B7 on the xenogeneic donor cells and CD28 on recipient T-cells. In a second aspect, co-stimulation is antagonised by expressing a ligand for CTLA-4 on the xenogeneic donor cells. This ligand binds to CTLA-4 on activated T-cells of the recipient and antagonises signal 2. In a third aspect, co-stimulation is prevented by expressing recipient organism MHC class II on the surface of the cells of the xenogeneic donor organ. The donor cells are thus able to present xenoantigens to a recipient T-cell in the context of self-MHC class II. If the donor cells do not express B7, or if B7 is blocked, the xenoreactive recipient T-cell becomes anergic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		